D11

Technical report

Key

	Reference	Subject matter and Comments
Annex 1	Manufacturing Batch Record: (F0001489703) I83K01 lot: I83G02	This document details the formulation and granulation process used for manufacturing the granule formulation to be used in 50mg capsules of 75% w/w sunitinib L-malate (internal code: SU10398).
Annex 2	Manufacturing Batch Record (F0001262959) lot: I83G02	This document details the capsule filling process used for manufacturing the 50mg capsules of 75% w/w sunitinib L-malate (internal code: SU10398) granules detailed in Annex 1. As noted on pages 20-21 granule adhesion occurred during capsule filling with this formulation. Indeed the capsule manufacturing process had to be frequently stopped due to the necessity to clean the equipment (hopper, dosators) each time from the granule blend that exhibited a high degree of adhesion to the equipment. Since the encapsulation process had to be stopped a number of times to clean the machine before continuing the process, it was decided that this formulation/process was not suitable for Final Registration of the formulation/drug manufacturing process for sunitinib.
Annex 3	Manufacturing Batch Record lot: I83G03	This document details the formulation, granulation and capsule filling processes used for manufacturing the 25mg capsules of 40% w/w sunitinib L-malate (internal code: SU10398) granules. As noted on page 29, granule adhesion did not occur during the capsule filling manufacturing process. However, the capsule filling machine was an old machine with a hopper design that periodically led to the discharge of powder from the powder bed meaning the machine had to be stopped at regular intervals to adjust the evenness of the powder bed in the capsule filling machine hopper so the process could continue. This problem was cured by mechanical adjustment and was not due to granule adhesion.

<table>
<tr>
<td>Annex 4</td>
<td>Stability Report

lot: I83G02</td>
<td>The dissolution and dissolution stability of the 50mg capsules of 75% w/w sunitinib L-malate (internal code: SU10398) granules prepared in Annex 2 were determined.

Page 3 summarises the 18 month timepoint data at 25°C/60%RH, pages 7-8 summarise the 12 month timepoint data at 25°C/60%RH and pages 13 - 14 summarise the initial timepoint data.

<table>
<tr><td rowspan="2">Stability timepoint</td><td colspan="3">Dissolution timepoint/ % release of API (%cv)</td></tr>
<tr><td>15 mins</td><td>30 mins</td><td>45 mins</td></tr>
<tr><td>Initial</td><td>97.7
(2.6%)</td><td>98.5
(1.4%)</td><td>99.5%
(1.7%)</td></tr>
<tr><td>12 month
25°C/60%RH</td><td>96.05</td><td>97.23
(2.75)</td><td>98.18%</td></tr>
<tr><td>18 month
25°C/60%RH</td><td>N/A</td><td>105.63
(2.22)</td><td>N/A</td></tr>
</table>
RH = relative humidity
API = sunitinib free base (SU-011248)
cv = coefficient of variation (relative standard deviation)

These data show that at the initial and 12 month stability timepoints after manufacture essentially all the drug was released from the formulation at all dissolution time points and the %cv data given shows that this was demonstrated in a reproducible manner across the capsule batch indicating blend homogeneity had been achieved. Additionally, after storage for 18 months, a comparable result was achieved. These results indicate that the dissolution profile was essentially unchanged on storage.

Such results are satisfactory and in principle would support Final Registration of the drug manufacturing process for this formulation of sunitinib malate.</td>
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<table>
<tr>
<td>Annex 5</td>
<td>Stability report

lot: I83G03</td>
<td>The dissolution and dissolution stability of the 25mg capsules of 40% w/w sunitinib L-malate (internal code: SU10398) granules prepared in Annex 3 were determined.

Pages 35, 38 and 39 summarise the 12 month timepoint data at 25°C/60%RH and pages 69 and 72 summarise the initial timepoint data.

<table>
<tr><td rowspan="2">Stability timepoint</td><td colspan="3">Dissolution timepoint/ % release of API (%cv)</td></tr>
<tr><td>15 mins</td><td>30 mins</td><td>45 mins</td></tr>
<tr><td>Initial</td><td>68</td><td>92.62
(7.59)</td><td>97.5</td></tr>
<tr><td>12 month
25°C/60%RH</td><td>77.24
(7.27)</td><td>94.62
(4.6)</td><td>97.39
(2.25)</td></tr>
</table>

RH = relative humidity
API = sunitinib free base (SU-011248)
cv = coefficient of variation (relative standard deviation)

These data show that at the initial stability timepoint after manufacture essentially all the drug was released from the formulation at the 45min. dissolution time point with the acceptance criteria also being met at the 30min. timepoint. Additionally, after storage for 12 months, a comparable result was achieved indicating that the dissolution profile was essentially unchanged on storage. Also, after storage for 12 months, the %cv data given at the 45min. dissolution timepoint shows that this was demonstrated in a reproducible manner across the capsule batch indicating blend homogeneity had been achieved.

Such results are satisfactory and support Final Registration of the drug manufacturing process for this formulation of sunitinib malate.</td>
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